DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

August 12, 2009

Docket No. FDA–2007–N–0475

Dear Midodrine Application Holder:

As you know, midodrine hydrochloride was approved under the Agency's accelerated approval regulations in 21 CFR part 314, subpart H on September 6, 1996. The New Drug Application (NDA) approval was based on a surrogate endpoint with the requirement that the sponsor complete phase 4 studies to verify the efficacy of midodrine in improving symptoms of patients with orthostatic hypotension as a condition of approval. To date, we have approved no application or supplement containing phase 4 study reports that verify the clinical benefit of midodrine hydrochloride. If an application or supplement containing studies that verify clinical benefit for midodrine hydrochloride is not approved in a timely manner as described herein, we will issue a Notice of Opportunity for a Hearing on the Center's proposal to withdraw the approval of the midodrine hydrochloride NDA (and all abbreviated NDAs (ANDAs) referencing that NDA) pursuant to 21 CFR §§ 314.530; 314.150, and 314.151.

As discussed in the March 8, 2007 joint meeting between the Agency and the midodrine application holders, to resolve the question of whether midodrine is effective, we require that you conduct further studies as described below.

Strategy
The requested studies will provide support for the efficacy of midodrine in improving symptoms of patients with orthostatic hypotension. Data will be derived from two randomized, double-blind, placebo-controlled studies.

- The first study should establish the effects of a single dose of midodrine on the symptoms of orthostatic hypotension. We recommend that subjects undergo a screening tilt table test prior to randomization to evaluate for the index disease. Subjects who do not develop symptoms of hypotension during the test should not be randomized.

- The second study should establish the presence of symptomatic benefit after at least two weeks of treatment. This trial could utilize a short period of randomized comparison of continued treatment versus placebo in the ≥ two week treatment population.

Both trials must be successful at a conventional ($p<0.05$) level of statistical significance for us to conclude that midodrine effectively relieves symptoms of orthostatic hypotension.

Labeling Changes
Appropriate sections of the label may be changed to incorporate the findings of the studies.

Reporting
You should submit the following data and information according to the specified timelines below. If the specified timelines are not met, the Center for Drug Evaluation and Research (CDER) will issue a Notice of Opportunity for a Hearing on its proposal to withdraw the approval of this application pursuant to 21 CFR 314.530.

Submit your documentation of IRB approval for both studies on or before February 12, 2010.

Submit your proposed statistical analysis plans for both studies on or before February 12, 2010.

Submit monthly reports of your study enrollment. You must have both studies at 50% enrollment by April 12, 2010. You must have both studies at 100% enrollment by June 12, 2010.

Submit full study reports of the requested trials on or before October 12, 2010. The study reports of the requested trials, including full analyses, assessment, and interpretation, must be submitted in the usual format. The submission must include electronic datasets for all trial data for these studies, preferably in electronic format submitted according to available guidance.

Reports of the studies must be submitted as a supplement to your current application or in a new application with the proposed labeling you believe would be warranted based on the data derived from these studies. Also send a copy of the cover letter of your submission, via fax or messenger to:

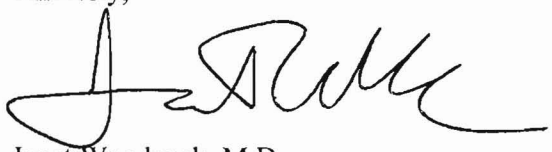
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
Attention: Norman Stockbridge, M.D., Ph.D., Director
10903 New Hampshire Avenue
Building 22, Room 4168
Silver Spring, MD 20993-0002

We look forward to working with you on this matter in order to obtain the data needed to establish the symptomatic benefit of midodrine in patients with orthostatic hypotension.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research